A Case of Thrombotic Thrombocytopenic Purpura Due to Clopidogrel: Case Report

Klopidogrele Bağlı Bir Trombotik Trombositopenik Purpura Olgusu

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ABSTRACT Thrombotic thrombocytopenic purpura (TTP) is a life-threatening multisystemic disease. We present a patient who has been diagnosed with clopidogrel-related TTP. A 53-year-old male patient presented with fever, blurring of consciousness and weakness in right half of his body. Percutaneous transluminal coronary angioplasty and stent implantation had been performed and clopidogrel had been started ten days ago. Before procedure, hemoglobin: 9.9 g/dL, platelet: 155000/µl, creatinine: 1.1 mg/dL, LDH: 350 U/l. On his admission, hemoglobin: 8.6 g/dL, platelet: 75000/µl, creatinine: 1.7 mg/dL, LDH: 1363 U/l, were detected". Peripheral blood smear showed polychromasia and distinct fragmented erythrocytes. The patient was diagnosed as TTP. Clopidogrel was discontinued. Prednisolone was started as 1 mg/kg/day. But after three days, thrombocytopenia and peripheral blood findings did not improve. Twenty-nine plasmapheresis were performed. The patient was discharged on thirtieth day

Key Words: Clopidogrel; purpura, thrombotic thrombocytopenic

ÖZET Trombotik trombositopenik purpura (TTP) yaşamı sınırlandırıcı multisistemik bir hastalıktır. İdiyopatik olduğu bilinirken, bazı immünosüpresif ve kemoterapötik ajanlar ve tiklopidin, klopidogrel gibi bazı antiplatelet ajanlar da TTP'ye yol açan ilaçlar olarak açıklanmıştır. Elli üç yaşında bir erkek hasta ateş, bilinç bulanıklığı ve vücudun sağ yarısında kuvvet kaybı ile bize başvurdu. On gün önce koroner anjiyoplasti ve stent implantasyonu yapılmıştı. İşlem öncesi, hemoglobin: 9.9 g/d;L, trombosit: 155000/µl, kreatinin: 1.1 mg/dL, LDH: 350 U/l idi. Geldiğinde, hemoglobin: 8.6 g/dL, trombosit: 75000/µl, kreatinin: 1.7 mg/dL, LDH: 1363 U/l olarak bulundu. Kan yaymasında Polikromazi ve belirgin fragmante eritrositler görüldü. Hasta TTP olarak teşhis edildi. Klopidogrel kesildi. Prednizolon 1 mg/kg/gün başlandı. Ama üç gün sonra, hastanın trombositopenisi ve periferal kan bulguları düzelmedi. Yirmi dokuz kez terapötik plazma değişimi yapıldı. Otuzuncu günde çıkarıldı.

Anahtar Kelimeler: Klopidogrel; trombotik trombositopenik purpura

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Thrombotic thrombocytopenic purpura (TTP) is a life-threatening multisystemic disease. It is characterized by fever, thrombocytopenia, microangiopathic hemolytic anemia, neurological findings, and renal dysfunction. The mortality rate prior to the use of plasma exchange was as high as 90 percent. However currently, mortality rate has decreased to 10-20%. While most of the TTP cases are known to be idiopathic, certain immunosuppressive or chemotherapeutic agents and some antiplatelet

agents such as ticlopidine, have also been described as TTP-inducing drugs.[1] Clopidogrel is an antiplatelet agent derived from thienopyridine. It displays a chemical structure and mechanism of action similar to ticlopidine. While ticlopidine-related TTP incidence is 1/1600-5000, clopidogrel-related TTP incidence is reported to be 1/20000.[2] We present a patient who has been diagnosed with clopidogrel-related TTP due to symptoms such as fever, anemia, thrombocytopenia, renal dysfunction, blurring of consciousness and weakness in right half of his body started after using clopidogrel for ten days.

CASE REPORT

A 53-year-old male patient presented with fever and blurring of consciousness. The patient had been subjected to percutaneous transluminal coronary angioplasty and stent implantation by coronary angiography ten days ago. Metoprolol 100 mg/d, acetyl salicylate 300 mg/d, and clopidogrel had been started. Before procedure, following results had been obtained: hemoglobin: 9.9 g/dL, hematocrit: 33%, MCV: 86 fl, MCH: 29 pg, MCHC: 33 g/dL, platelet: 155000/µl, leukocyte: 6500/µl, BUN: 13 mg/dL, creatinine: 1.2 mg/dL, LDH: 350 U/l. No complication had been detected after the procedure and patient had been discharged. However, the patient applied ten days after the angiography due to fever, blurring of consciousness, and weakness in right half of his body. He was in stupor while he came to our unit. He was responding to painful stimulants but verbal communication could not be established. Motor aphasia and right hemiparesis with predominant brachiofacial involvement was determined. There was no sign of petechia or ecchymose. Other systemic examinations were normal. Arterial blood pressure was 110/70 mmHg, pulse was 90/min, and body temperature was 38 ˚C. The remaining test results were found to be as follows; hemoglobin: 8.6 g/dL, hematocrit: 26.4%, MCV: 86.8 fL, MCH: 29.9 pg, MCHC: 34.5 g/dL, platelets: 75000/µl, corrected reticulocyte: 3.8%, haptoglobin: 15 mg/dL (20-302), leukocyte: 8400/µL, BUN: 25 mg/dL, creatinine: 1.7 mg/dL, LDH: 1363 U/l, CK: 532 U/l (38-174), CRP: 6 mg/l (0-5), prothrombin time: 14.3", aPTT: 28.3", INR: 1.04. Peripheral blood smear showed polychromasia and distinct fragmented erythrocytes. Direct Coombs test was negative. Non-contrast cranial CT was normal.

The patient was diagnosed as TTP due to presence of microangiopathic hemolytic anemia, thrombocytopenia, neurological findings, renal dysfunction, and fever. Clopidogrel was discontinued. Prednisolone was started at 1 mg/kg/day. After three days, the results were as follows: hemoglobin: 8.8 g/dL, hematocrit: 24%, platelet: 16000/µl, leukocyte: 9400/µl, creatinine: 1.8 mg/dL, LDH: 2574 U/l, total bilirubin: 1.95 mg/dL, indirect bilirubin: 1.47 mg/dL. Repeated peripheral blood smear revealed fragmented erythrocytes and schistocytes. Therapeutic plasma exchange (TPE) was performed. Following the first TPE, patient regained his consciousness and platelet count was reached to 23000/µl. While the number of platelets continued to increase; indirect bilirubin, LDH, and creatinine counts showed a gradual decrease. Because after five plasmapheresis platelet count surpassed 100000/µl, plasmapheresis was discontinued. However, plasmapheresis was started to be applied daily again when the platelet count dropped to 53000/µl and LDH reached to 924 U/I. Twenty nine TPE required. The patient was discharged due to improvement of the microangiopathic hemolytic anemia and clinical signs on thirtieth day.

DISCUSSION

Drugs are responsible for approximately 10-15% of all TTP cases. Antineoplastic drugs (particularly mitomycin), cyclosporin, tacrolimus, muromonab-CD3 (OKT3) and interferons, and other drugs such as antiagregant agents (ticlopidine, clopidogrel) and quinine, can cause TTP.[3] Clopidogrel-related TTP usually develops within the first 2 weeks after administration of the drug. However, it has been reported to develop at the 72th hour following a 300 mg loading dose.[4] Rarely, it may develop 1 year after the application of the drug. In the present case, thrombocytopenia and hemolytic anemia developed at the 10th day of the clopidogrel therapy.[5,6]

Solely thrombocytopenia has been detected to be associated with clopidogrel.[7]

Idiopathic TTP, develops via IgG autoantibodies formed against the metalloproteinase (vWF "cleaving" enzyme) which cleaves von Willebrand factor (vWF). Eventually, the vWF accumulated in the blood stream binds to glycoprotein receptors Ib/IX/V and IIb/IIIa which are localized on the surface of platelets, and forms thrombocyte microthrombi in capillary and arteriolar vessels. Those events are followed by systemic arteriolar thrombosis. The metalloproteinase mentioned here belongs to the ADAMTS (A Disintegrin and Metalloproteinase domain, with ThromboSpondin type 1 motif), and called as ADAMTS13. The presence of autoantibodies is an important feature which distinguishes TTP from hemolytic uremic syndrome. Therefore, ADAMTS13 level in HUS is normal. While the autoantibodies against ADAMTS13 have been found in idiopathic TTP cases, they were shown to be present only in a few of cases with TTP associated with ticlopidine and clopidogrel. Thus, the underlying pathology of TTP cases associated with ticlopidine and clopidogrel, are not clear yet. However, in a series including 11 cases with ticlopidine-related TTP, 5 cases have been shown to cause apoptosis in dermal, glomerular, hepatic microvascular endothelial cells (MVEH) (not in pulmonary MVEH and large vascular endothelial cells) leading to a decrease in the amount of thrombospondin-1 transcription which is known to be an extracellular matrix component.[8,9]

Early diagnosis in drug-related TTP is a life-saving measure. The preferred treatment is TPE. As a result of the plasma exchange, the patient is given metalloproteinase within the fresh frozen plasma and the IgG autoantibodies formed in plasma against this enzyme are removed.[10] Survival rate has been reported to be better in patients who were put on TPE treatment within the first 3 days following the occuring of clinical signs compared to that of patients who received TPE treatment following more than 3 days from the start of the clinical symptoms.[5] The number of mean TPE session has been reported to be eight.[2] The highest number of reported TPE sessions on 1 patient, was 17.[11] In our case, we started TPE on the 2nd day following occurrence of clinical symptoms. We applied 29 TPE sessions. While corticosteroids are reported to be helpful particularly in cases with high rate of anti-ADAMTS13 antibodies, their efficiency in drug-related cases is obscure. Clopidogrel-related TTP cases rarely exhibit recurrence. Failure of diagnosis and eventually absence of early-period plasmapheresis treatment, increase the mortality.

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